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Evaluation of NSAIDs for treating post-endodontic pain

A systematic review

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Although many studies have evaluated analgesic strategies for control of postendodontic pain, there have been no systematic reviews of this literature. This article describes the process for conducting a systematic review and uses this method to analyze the use of non-steroidal anti-inflammatory drugs (NSAIDs) for treatment of postendodontic pain.

Many endodontic patients believe that post-treatment pain is unavoidable, yet several clinical trials indicate that postoperative pain occurs in only 25–40% of all endodontic patients (1–4). However, post-treatment pain may last up to several days, depending upon peripheral and central mechanisms of hyperalgesia (5–7). Hence, successful management of endodontic pain is an important concern for patients and clinicians.

Although many recommendations have been given for the use of analgesics in treating postendodontic pain, no study has used the method of systematic review to analyze clinical endodontic trials and provide an evidence-based recommendation for treatment. The purpose of this study therefore is to systematically review the endodontic literature evaluating the use of non-steroidal anti-inflammatory drugs (NSAIDs) in pain management following endodontic therapy.

NSAIDs were selected for several reasons. First, pulpal inflammation and necrosis, and the corresponding periradicular tissue changes cause the release of inflammatory mediators, including prostaglandins, which are involved in the mediation of pain (8). Thus, the rationale for the pharmacological management of postendodontic pain is focused on the reduction of chemical inflammatory mediators that activate or sensitize peripheral nociceptors and the subsequent events involved in pain perception. For example, specific interventions can include the NSAID inhibition of prostaglandins, steroid inhibition of multiple inflammatory mediators, local anesthetic inhibition of sodium channels, and opioid suppression of central nociceptive processing (9). Prostaglandin suppression is particularly important because administration of prostaglandin lowers the pain threshold (i.e. produces allodynia) and sensitizes nociceptors to other pain mediators (10). Second, although prostaglandins are only one of many pro-nociceptive inflammatory mediators, it is important to realize that their tissue levels are associated with patient reports of pain (8, 11), suggesting that NSAIDs may be key drugs for inflammatory pain abatement. Third, NSAIDs are widely available without prescription, and some studies suggest that NSAIDs are effective in managing endodontic pain (2, 12). However, to date there are no systematic reviews of the literature on NSAID analgesia in postendodontic pain patients.

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Methods

A MEDLINE search strategy (Table 1) was developed to identify articles dealing with pain and endodontics.

The search included articles in MEDLINE from 1966 to November Week 1, 2000. Of the 59 articles that fulfilled these search criteria, those dealing with pain management following endodontic therapy were selected based on a review of the titles and abstracts by two reviewers.

The identified articles were then screened and those with at least one NSAID treatment group and a control group were selected for closer examination. These studies were reviewed for inclusion based on the following criteria:

- subjects underwent non-surgical root canal treatment;
- the NSAID was administered orally;
- a placebo control group was employed;
- baseline pain levels were measured numerically;
- outcome data were stated;
- there was randomized assignment of treatment groups.

Validity of the identified articles was assessed according to previously established criteria (13).

The five studies that met the above criteria were selected for detailed analysis (Table 2). Extracted data included the types of drugs and control groups used, the number of subjects in each group, the times at which pain was evaluated, the dose and timing of drug administration, and the outcome variables used to measure pain levels. Although the five studies sampled numerous outcome measurement time points, only the three time points in common among all studies were examined in the analysis (baseline, 6, and 24 h).

Data from the studies were plotted using L'Abbe graphs for comparative visual analysis. The 45° line in these graphs represents a line of equivalence in which the variables plotted on the *X*- and *Y*-axes produce the same effect. We have used two separate L'Abbe plots to analyze the data from these studies.

In the first L'Abbe analysis (Fig. 1), we plotted the baseline pain values on the *X*-axis and the postoperative pain values (either 6 or 24 h) on the *Y*-axis. In this graph, the 45° line indicates that the treatment (placebo or experimental analgesic) resulted in the same level of pain at baseline and at the postoperative time points (6 or 24 h). Symbols below and to the right of the line of equivalence indicate that the treatment produced *less pain* at the 6 or 24 h time point as compared to baseline values. Conversely, symbols to the left and above the line of equivalence indicate that the treatment resulted in *greater pain* at the 6 or 24 h time point as compared to baseline values. Symbols for a given study that are roughly above or below one another indicate a similar baseline for each group. Conversely, symbols for a given study that are substantially right or left of one another suggest that the groups were not equivalent at the baseline. Thus, this type of L'Abbe analysis permits evaluation of how well each study randomized baseline pain levels across the treatment groups. Each study is represented by a similar set of colored symbols (e.g. the Doroschak et al. study from 1999 is represented by blue circles, each of the different shapes represent each of the treatment groups studied).

Table 1. MEDLINE search strategy developed to find articles related to pain management following endodontic therapy (1966 to November Week 1, 2000)

Step #	Search History	Results
1	toothache/	1260
2	endodontics/or dental pulp capping/or pulpectomy/or pulpotomy/ or 'root canal therapy'.mp [mp = title, abstract, registry number word, mesh subject heading]	12 028
3	1 or 2	13 142
4	Pain/or pain, intractable/or pain measurement/or pain, postoperative/or pain threshold/	72 578
5	3 and 4	395
6	limit 5 to (human and English language and (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or randoormized controlled trial))	59

Table 2. Studies included with summary of selected variables

Author/ Date	Treatment Groups	*N** (C)	*N* (E1)	*N* (E2)	*N* (E3)	*N* (E4)	Time(s) of pain evaluation	Outcome variable	Inclusion criteria	Treatment	Dose/ Timing (C)	Dose/ Timing (E1)	Dose/ Timing (E2)	Dose/ Timing (E3)	Dose/ Timing (E4)
Doroschak et al. 1999 (12)	Placebo (C), Tramadol (E1) Flurbiprofen (E2) Flurbiprofen/ Tramadol (E3)	12	12	12	13		Baseline, 6 h; 1, 1.5, 2, 2.5 d**	VAS	Endodontic emergency treatment required (spontaneous pain, vital/ nonvital)	Emergency endodontic treatment	1 cap post treatment, 1 cap q6 h	100 mg post treatment, 100 mg q6 h	100 mg post treatment. 50 mg q6 h	100 mg/100 mg post treatment, 50 mg/100 mg q6 h	
Rogers et al. 1999 (14)	Placebo (C), Ibuprofen (E1)	12	12				Baseline, 6, 12, 24, 48 h**	VAS	RCT required, vital pulp	2 visit RCT	Following first visit	600 mg following first visit			
Battrum & Gutman 1996 (17)	RCT only (C), Ketorolac (E1)	10	10				Baseline, 6, 24 h**	VAS	RCT required, recognized endodontic diagnosis	1 or 2 visit RCT	None	10 mg at treatment time, q6 h for 24 h			
Torabinejad et al. 1994 (7)	Placebo (C), Ibuprofen (E1), Salicylic Acid (E2), Acetaminophen (E3)	41	48	43	45	39	Baseline, 6, 12, 18, 24, 30, 36 h**	Modified VAS	RCT required, symptomatic/ asymptomatic, pulpal/complete periapical pathosis	Previously cleaned/ shaped canals, complete obturation	1 cap. post treatment, 1 cap. q6 h for 66 h	400 mg post treatment, 400 mg q6 h 650 mg of q6h	650 mg post treatment, for 66 h	650 mg post treatment, 650 mg q6 h for 66 h	50 mg post treatment 50 mg q6 h for 66 h
Flath et al. 1987 (15)	Placebo/Placebo (C), Flurbiprofen/ Flurbiprofen (E1), Placebo/ Flurbiprofen (E2), Flurbiprofen/ Placebo (E3)	29	29	30	28		Baseline, 0, 3, 7, 24 h**	VAS	RCT required, symptomatic/ asymptomatic	Pulpectomy	Pretreatment, 3 h post treatment	100 mg pretreatment 100 mg, 3 h post treatment	Pretreatment, 100 mg 3 h post treatment	100 mg pretreatment 3 h post treatment	

N = number of subjects in treatment group. (C) = placebo control. (E) = experimental drug treatment.
** Times stated are post treatment time intervals at which pain scores were evaluated. Baseline refers to pretreatment (initial) pain score.

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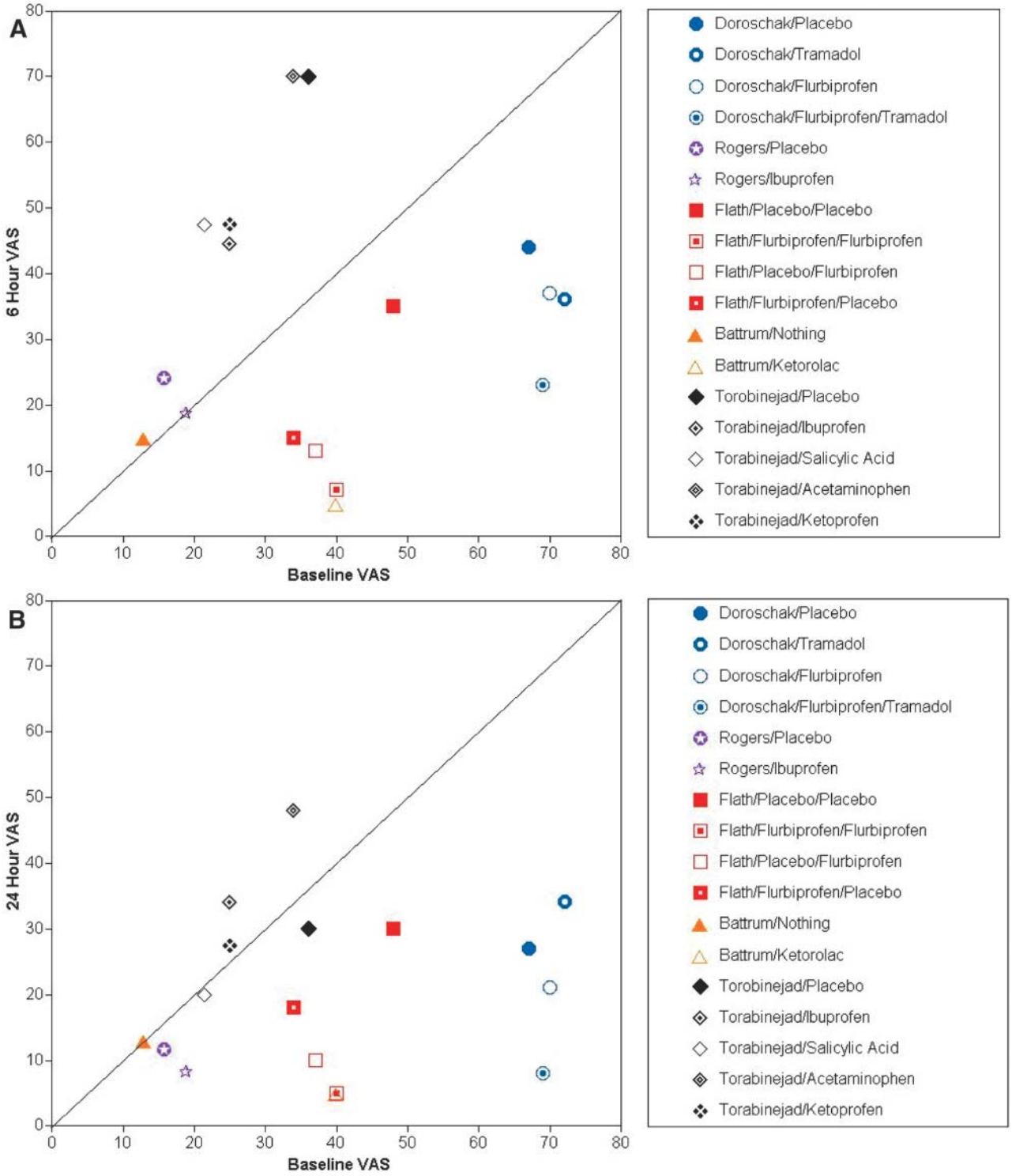

Fig. 1. L'Abbe plots of the pain intensity at baseline compared to pain intensity at 6 h (Panel A) and 24 h (Panel B) time points. In this graph, the 45° line of equivalence indicates that the treatment (placebo or experimental analgesic) resulted in the same level of pain at baseline and at the postoperative time points (6 or 24 h). Symbols below and to the right of the line of equivalence indicate that the treatment produced *less pain* at the 6 or 24 time point as compared to baseline values. Conversely, symbols to the left and above the line of equivalence indicate that the treatment resulted in *greater pain* at the 6 or 24 h time point as compared to baseline values. Studies are represented by a similar set of colored symbols (e.g. the Doroschak et al. (12) study from 1999 is represented by blue circles, each of the different shapes represent each of the treatment groups studied).

The second L'Abbe analysis (Fig. 2) provides a visual presentation of the relative superiority of the analgesics compared with placebo treatment. To create this graph, we first calculated the change in pain intensity from the baseline value to pain levels measured at 6 h and 24 h post-treatment. A reduction in pain was assigned a negative score, whereas an increase in pain intensity was given a positive score (see the scales on the *X*- and *Y*-axes in Figs 1 and 2). The change in pain intensity for the placebo treatment is plotted along the *X*-axis, and the change in pain intensity for the experimental drug treatments are plotted along the *Y*-axis. In this graph, the 45° line indicates equivalence between the placebo control and the experimental drug (i.e. the same changes in pain intensity occurred with both treatments). Symbols below and to the right of the line of equivalence indicate that the experimental analgesic provided *greater analgesia* than the placebo treatment. Conversely, symbols to the left and above the line of equivalence indicate that the experimental treatment provided *less analgesia* than the placebo treatment. Thus, this type of L'Abbe analysis permits interpretation of how well the analgesics worked in each study as compared to their placebo treatment.

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Results

The MEDLINE search strategy identified 59 articles (Table 1). Articles dealing with pain management following endodontic therapy were selected based on title and abstract. Thirteen studies had at least one NSAID treatment group and five studies met our *a priori* inclusion-exclusion/study design criteria.

Examination of the L'Abbe analysis of the 6- and 24-h VAS scores vs. baseline VAS plots showed considerable variability among the trials (Fig. 1). This included variability in four dimensions:

1 Horizontal dispersion of (baseline) pain levels (suggesting variation in inclusion and exclusion criteria or differences in patient populations). For example, the Battrum/Nothing and the Battrum/ketorolac groups show comparatively large horizontal differences in baseline pain values as compared to the other four studies in Fig. 1A.

2 Vertical dispersion within a trial (suggesting differences in effectiveness of the drugs). For example, the Flath/placebo and Flath/flurbiprofen groups display relatively large vertical differences, suggesting effectiveness for flurbiprofen analgesia in Fig. 1A.

3 Symbols above the 45° equivalence line (suggesting either that the pharmacological treatment did not produce analgesia or that the endodontic treatment increased pain levels). For example, the Torabinejad/placebo and Torabinejad/acetaminophen groups are plotted well above the 45° line of equivalence in Fig. 1A, suggesting that neither intervention resulted in pain reduction.

4 Symbols plotted below 45° line (suggesting either that the drugs produced analgesia or that the endodontic treatment reduced pain). For example, the Flath/flurbiprofen and Doroschak/flurbiprofen/tramadol groups are plotted well below the 45° line of equivalence in Fig. 1B, suggesting that both interventions reduced postendodontic pain.

Several general conclusions can be drawn from this analysis of the 6 h data. At the 6 h time point (Fig. 1A), the symbols for the Torabinejad et al. (7) and Rogers et al. (14) studies are above the 45° line, indicating that there was more pain at 6 h than at baseline. In contrast, the symbols for the Flath et al. (15) and Doroschak et al. (12) studies are below the 45° line, indicating that there was pain abatement at 6 h. Also interesting is the low baseline VAS of the first two studies and the high baseline of the latter two studies. This suggests that patients in the latter two studies were in greater pain at baseline than in the former two studies. Also notable in four of these five studies, all of the markers for a given study are generally above one another, indicating that the baseline VAS scores for the different groups in each study were generally similar. In addition, patients presenting with moderate-to-severe preoperative pain (i.e. baseline VAS ≥ 40) responded to placebo treatment (i.e. endodontic therapy with placebo medication), whereas this was not observed with patients having less baseline pain (i.e. baseline VAS < 40). Importantly, in patients presenting with moderate-to-severe preoperative pain (i.e. baseline VAS ≥ 40), the addition of an active pain medications reduced pain levels more than placebo treatment. Among those tested, the most effective were: the flurbiprofen/tramadol combination (12) and the preoperative flurbiprofen/postoperative flurbiprofen regimen (15).

Data for the 24 h pain levels are presented in Fig. 1B. At this time point, all of the symbols, with the exception of the Torabinejad et al. (7) experimental

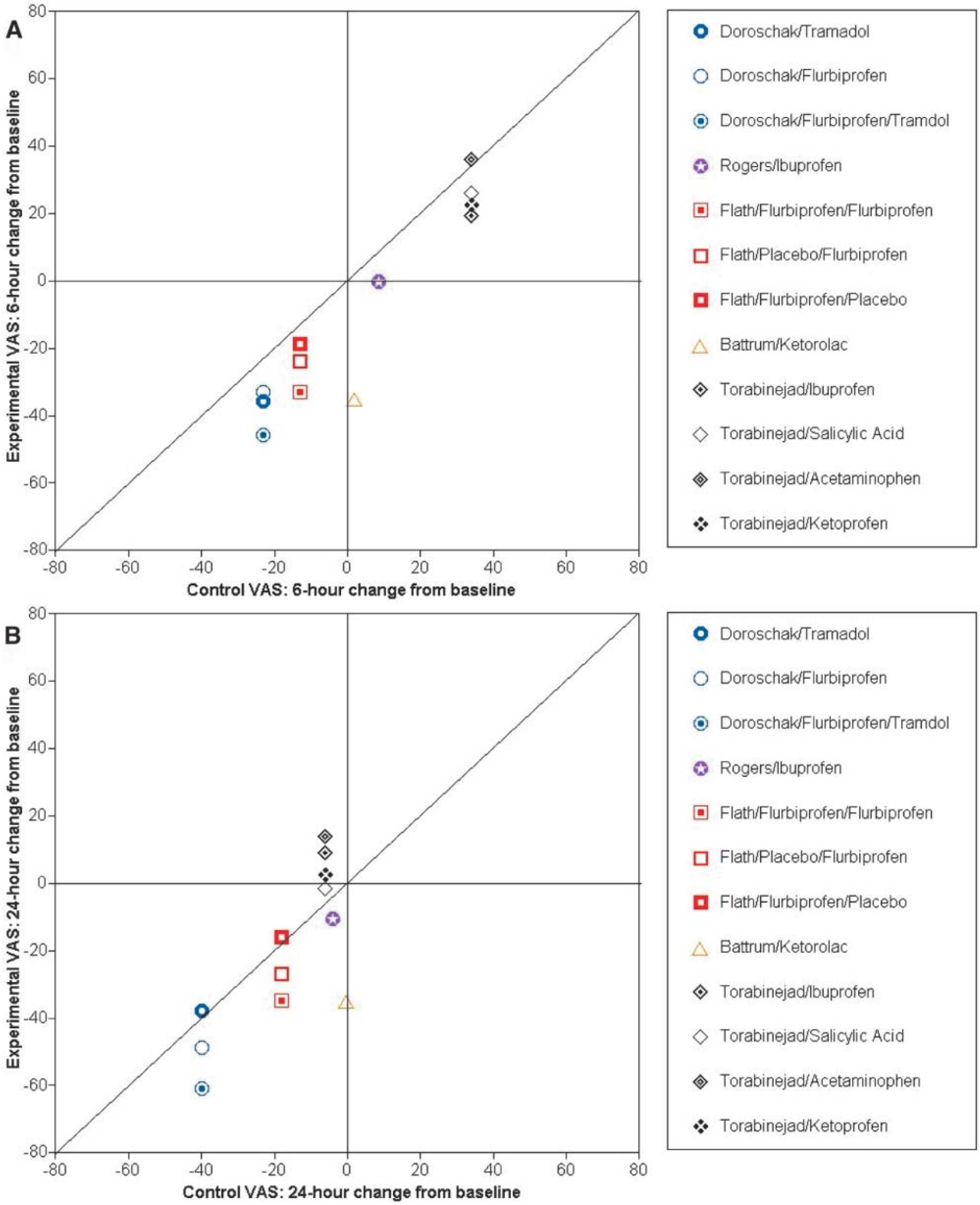

Fig. 2. L'Abbe plots of the change in pain intensity from baseline values to 6 h (Panel A) and 24 h (Panel B) pain values. Changes in pain after placebo treatment are plotted on the ordinate and changes in pain after experimental analgesic treatment are plotted on the abscissa (negative difference scores represent pain reduction and positive difference scores represent an increase in pain). In these graphs, the 45° line indicates equivalence between the placebo control and the experimental drug (i.e. same changes in pain intensity occur with both treatments). Symbols below and to the right of the line of equivalence indicate that the experimental analgesic provided *greater analgesia* than the placebo treatment. Conversely, sym-

groups, are below the 45° line, indicating that there was pain abatement compared to baseline levels. For all groups, the VAS scores are below where they were at 6 h, indicating that there was less pain at 24 h. Further, the drugs that were most effective at 6 h remained effective at 24 h. That is: the preoperative flurbiprofen/postoperative flurbiprofen regimen (15) and the flurbiprofen/tramadol combination (12).

To determine whether the analgesic treatments were superior to placebo, we next calculated the differences in pain levels from baseline values to levels obtained at 6 h (Fig. 2A) and 24 h (Fig. 2B) after treatment. At 6 h (Fig. 2A), 11 treatment groups are to the right of the equivalence line, indicating that the patients given active analgesics had less pain than patients given placebo treatment. Also noteworthy, approximately half of the symbols are above 0 on both the *X*- and *Y*-axis, and half are below 0 on both axes. Those symbols above 0 indicate an increase in pain at 6 h, while symbols below 0 indicate a decrease in pain at 6 h. Thus, in the Torabinejad study, while the medicated patients are to the right of the line of equivalence (indicating that the medicated patients had less pain than controls), all the symbols are above 0 on the *X*-axis (indicating that the control subjects had increased pain at 6 h as compared to baseline levels). Further, the symbols are above 0 on the *Y*-axis, indicating that the medicated groups in this study had increased pain at 6 h. These results can be contrasted with the results of Doroschak et al. (12) and Flath et al. (15), where all the symbols are right of the equivalence line and below 0 on both the *X*- and *Y*-axis. These latter results indicate that the medicated patients had less pain than the placebo control patients and that both groups had less pain at 6 h than at baseline.

Differences were also apparent at the 24 h time point (Fig. 2B). At 24 h, only 6 symbols are to the right of the equivalence line, and all 6 are below 0 on the *X*- and *Y*-axis. Of these, the flurbiprofen/tramadol combination (12) and the preoperative flurbiprofen/postoperative flurbiprofen regimen (15) appear to be most effective in pain control. Also notable at 24 h, more symbols are above the equivalence line than at 6 h, indicating that the medicated groups had more pain than the the placebo control patients at this time point for these medications in these studies. This is consistent with the observation that all symbols are below 0 on the *X*-axis. Further, with the exception of ibuprofen, acetaminophen, and ketoprofen (7), all symbols are also below 0 on the *Y*-axis, indicating that the remaining medicated patients had less pain at 24 h than at baseline.

Discussion

Ibuprofen is the most frequently used NSAID for control of pain associated with root canal treatment (16). This endodontic application of ibuprofen is consistent with the results of systematic reviews carried out by the Pain Research Unit, Department of Anesthesia, Churchill Hospital, and the University of Oxford. The Pain Research Unit is internationally recognized for its comprehensive systematic review of many analgesic trials evaluating numerous drugs, dosages and pain conditions (see *http://www.jr2.ox.ac.uk/bandolier/booth/painpag/*for further details).

Table 3 summarizes the results of the Pain Research Unit/Oxford League for analgesic efficacy. Two analgesic outcome measures are provided for each drug. First, the 'Percent >50% pain relief' refers to the proportion of treated patients who report ≥50% pain relief over a 4–6-h period as compared with patients taking a placebo. This is a useful clinical outcome measure since it provides clinicians with a practical way of comparing various analgesic drugs. The second outcome measure is the number needed to treat (NNT). The NNT is the number of patients needed to treat with an active medication in order to obtain one patient with a better outcome than a placebo medication. Thus, the lower the NNT value, the better the drug is as an analgesic. The NNT value thus represents a measure of the superiority of an experimental analgesic over a placebo treatment and permits direct comparison of results across studies (since the results from experimental treatment is normalized to the placebo group from its own study). The 95% confidence intervals for the NNT are also

bols to the left and above the line of equivalence indicate that the experimental treatment provided *less* analgesia than the placebo treatment. Studies are represented by a similar set of colored symbols (e.g. the Doroschak et al. (12) study from 1999 is represented by blue circles, each of the different shapes represent each of the treatment groups studied).

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Table 3. Oxford League table of Analgesic Efficacy. Analgesics listed from most to least effective, based on number needed to treat. The number needed to treat (NNT) refers to the number of patients that need to be treated for one patient to have a significant decrease in pain. Thus, the lower the NNT, the more effective the drug. NNT is calculated for the proportion of patients with at least 50% pain relief over 4–6 h compared with placebo in randomized, double-blind, and single-dose studies in patients with moderate to severe pain. Drugs were oral, and doses are milligrams. (From: *http://www.jr2.ox.ac.uk/bandolier/booth/painpag/*)

Analgesic	*N*	% >50% pain relief	NNT	Lower confidence interval	Upper confidence interval
Ibuprofen 800	76	100	1.6	1.3	2.2
Ketorolac 20	69	57	1.8	1.4	2.5
Ketorolac 60	116	56	1.8	1.5	2.3
Diclofenac 100	411	67	1.9	1.6	2.2
Piroxicam 40	30	80	1.9	1.2	4.3
*Acetaminophen 1000+Codeine 60	197	57	2.2	1.7	2.9
Oxycodone IR 5 +aracetamol 500	150	60	2.2	1.7	3.2
Bromfenac 25	370	51	2.2	1.9	2.6
Rofecoxib 50	675	54	2.3	2.0	2.6
Diclofenac 50	738	63	2.3	2.0	2.7
Naproxen 440	257	50	2.3	2.0	2.9
Oxycodone IR 15	60	73	2.3	1.5	4.9
Ibuprofen 600	203	79	2.4	2.0	4.2
Ibuprofen 400	4703	56	2.4	2.3	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Bromfenac 100	95	62	2.6	1.8	4.9
Oxycodone IR 10 +Acetaminophen 650	315	66	2.6	2.0	3.5
Ketorolac 10	790	50	2.6	2.3	3.1
Ibuprofen 200	1414	45	2.7	2.5	3.1
Oxycodone IR 10 +Acetaminophen 1000	83	67	2.7	1.7	5.6
Piroxicam 20	280	63	2.7	2.1	3.8
Diclofenac 25	204	54	2.8	2.1	4.3
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Bromfenac 10	223	39	2.9	2.3	4.0
Demerol 100	364	54	2.9	2.3	3.9
Tramadol 150	561	48	2.9	2.4	3.6
Morphine 10	946	50	2.9	2.6	3.6
Naproxen 50	169	46	3.0	2.2	4.8
Naproxen 220/250	183	58	3.1	2.2	5.2
Acetaminophen 500	561	61	3.5	2.2	13.3
Acetaminophen 1500	138	65	3.7	2.3	9.5

provided; analgesics that overlap within their 95% confidence intervals are statistically indistinguishable. Also informative, the reported studies used a standard outcome measure for success (at least 50% pain relief after 4–6 h), and a standard measuring instrument (100 point VAS). These study design factors facilitate systematic review across studies and should be considered whenever endodontic pain studies are being designed.

Their systematic review indicates that the 800 mg dosage of ibuprofen was the most effective drug in reducing acute pain in 4–6 h. Further, there is a dose–response, with increasing analgesic effectiveness as the dose of ibuprofen increases from 50 mg to 800 mg (*http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/AP012.html*) (Fig. 3).

Effective pain control in endodontics represents a hallmark of clinical excellence. Accordingly, it is important to conduct randomized controlled trials that evaluate analgesic interventions in endodontic pain patients. The present study represents, to our knowledge, the first systematic review of the use of NSAIDs in treating endodontic pain.

Several general conclusions on experimental design can be made from our analysis. First, there were only a limited number of randomized clinical trials available on this topic with comparatively minimal overlap among the types of drugs used in these studies. Future studies may wish to include both a placebo control and a standard positive control (e.g., ibuprofen 800 mg) to facilitate direct comparison among studies. Second, there was a lack of uniformity among studies with respect to times at which pain was evaluated. To facilitate comparisons in this review, com-

Table 3 continued

Analgesic	*N*	% >50% pain relief	NNT	Lower confidence interval	Upper confidence interval
Acetaminophen 1000	2759	46	3.8	3.4	4.4
Oxycodone IR plus; Acetaminophen 1000	78	55	3.8	2.1	20.0
Acetaminophen 600/650+Codeine 60	1123	42	4.2	3.4	5.3
Ibuprofen 100	396	31	4.3	3.2	6.3
Acetaminophen 650 + Dextropropoxyphene 65 hydrochloride or 100 mg napsylate)	963	38	4.4	3.5	5.6
Aspirin 600/650	5061	38	4.4	4.0	4.9
Acetaminophen 600/650	1886	38	4.6	3.9	5.5
Ibuprofen 50	316	31	4.7	3.3	7.9
Tramadol 100	882	30	4.8	3.8	6.1
Tramadol 75	563	32	5.3	3.9	8.2
Aspirin 650 +Codeine 60	598	25	5.3	4.1	7.4
Oxycodone IR 5 +Acetaminophen 325	149	24	5.5	3.4	14.0
Acetaminophen 300 +Codeine 30	379	26	5.7	4.0	9.8
Bromfenac 5	138	20	7.1	3.9	28.0
Tramadol 50	770	19	8.3	6.0	13.0
Codeine 60	1305	15	16.7	11.0	48.0
Placebo	>10 000	18	N/A	N/A	N/A

*Acetaminophen is also known as paracetamol

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parisons were made at time points common to all studies, thus analysis was done only at baseline, 6, and 24 h. Third, the use of different outcome variables for pain measurement was evident. All five studies used the VAS or modified VAS, and analysis was based solely on this pain scale. Three studies, however, used other types of pain scales (12, 15, 17). However, none of the studies reported the number of subjects with a 50% reduction in pain. Uniform collection of pain scores using a 100-mm VAS and calculation of the number of subjects in each group reporting at least 50% reduction in pain would greatly increase the contribution of each study to the endodontic literature. Fourth, the study sample sizes ranged from 10 to 48, and none provided power calculations. Thus type I errors (identifying a difference when none exists) or type II errors (failing to identify a difference when it occurs) may occur in the reported results. Fifth, a major concern was the difference in inclusion and exclusion criteria of each of the studies. Standardized inclusion and exclusion criteria would facilitate generation of comparable results. Sixth, studies differed in the doses and timing of drug administration. One study in particular (15) evaluated the effect of pretreatment administration of analgesic medication. The other studies used standard post-treatment regimens. Thus, differences among studies might be due to differences in drug effect, or to differences due to experimental design. Establishing standardized experimental designs would avoid this problem and result in the generation of high quality data permitting clinicians to select optimal analgesics for control of postendodontic pain.

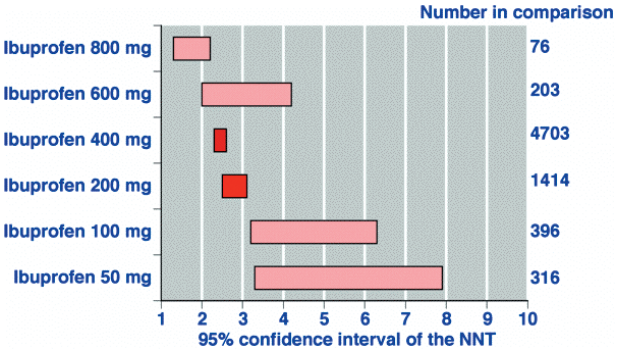

Fig. 3. Dose-response for ibuprofen compared with placebo. The number needed to treat (NNT) refers to the number of patients that need to be treated for one patient to have a significant decrease in pain. The lower the NNT the more effective the drug. The data indicates that 800 mg ibuprofen is the most effective drug in pain abatement (DATA from Table 3). From: *http://www.jr2.ox.ac.uk/bandolier/booth/painpag/acutrev/analgesics/ap012.html*

Several conclusions can also be made for treating endodontic pain patients. For example, endodontic therapy alone is thought to result in a significant degree of pain relief for those patients with pretreatment pain: on average, endodontic therapy with placebo treatment resulted in >50% pain reduction by one day post-treatment and about 90% by 2 days (12). Similarly, in this study, both the medicated and control patients had decreased pain levels. Thus, patients might perceive that any of the medications reduced pain at 6 and 24 h (Fig. 1), when in fact it could be that the treatment relieved pain. This emphasizes the need for including placebo control groups in clinical trial design.

The intensity of baseline pain appears to be an important factor in these studies and the best predictor of postoperative pain may be the presence of preoperative pain (15, 19). Patients who had mild preoperative pain experienced an increase in pain levels in the postoperative period. In contrast, patients with moderate-to-severe preoperative pain, reported significant reductions in postoperative pain after given the combination of endodontic treatment +preoperative NSAID, or endodontic treatment +NSAID/opioid combinations. For example, in the Flath et al. (15) study, patients had moderate-to-severe pain at baseline and they all had less pain following treatment. This is in contrast to the situation in which patients had no or mild pretreatment pain; in these studies, pain levels subsequently increasing following treatment (7). The data indicate that, relative to the controls (Figs 1A and 2A), the medicated patients actually experienced less pain.

The use of drug combinations may have synergistic effects by targeting different pharmacological pathways. This may factor may contribute to the significant analgesic effect of the tramadol/flurbiprofen combination (12). Tramadol hydrochloride is a drug approved by the U.S. Food and Drug Administration for the treatment of moderate to moderately severe pain. It is a centrally acting analgesic that acts as both an opioid agonist and a reuptake inhibitor of serotonin and norepinephrine (18).

In conclusion, controlled clinical trials examining acute and long-term postendodontic treatment pain are limited, as determined by searching MEDLINE. The review is limited to literature that is widely avail-

able to the U.S. clinician. Searches of neither the Cochrane database of controlled clinical trials, nor EMBASE or LILACs were carried out. Thus other well-controlled clinical trials could have well been missed in this review.

- Given these limitations, the identified studies suggest that NSAIDs are effective for treating endodontic pain, and;
- the most effective analgesics are a combination of flurbiprofen and tramadol or a combined regimen of preoperative and postoperative flurbiprofen.

However, before implementing this combination of drugs, the clinical community would be best served by a well-controlled clinical trial that

- compares the best NSAID pain medication demonstrated in other clinical trials (800 mg ibuprofen) with the most effective combination of drugs from this study (tramadol and flurbiprofen combination and/or pre- and post treatment flurbiprofen);
- uses a common baseline, 4–6 h and 24 h outcome time period;
- uses a 100 point VAS;
- assesses the number of patients who achieve a pre to post-treatment pain reduction of 50% or more.

Adoption of these study design issues will likely yield important insights into the effective control of post-endodontic pain.

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